ABSTRACTS

This section of the Journal is published in collaboration with the two abstracting Journals, Abstracts of World Medicine and Ophthalmic Literature, published by the British Medical Association. The abstracts are divided into the following sections: Syphilis (Clinical, Therapy, Serology, Pathology, Experimental), Gonorrhoea, Non-Gonococcal Urethritis and Allied Conditions, Chemotherapy, Public Health and Social Aspects, Miscellaneous. After each subsection of abstracts follows a list of articles that have been noted but not abstracted. All subsections will not necessarily be represented in each issue.

SYPHILIS (Clinical)

Cardiovascular Syphilis in Neurosyphilitic Patients. [In English.] RAASCHOU-NIELSEN, W., and KOPP, H. (1957). Acta derm.-venereol. (Stockh.), 37, 446. Bibl.

The authors have studied the incidence of cardiovascular syphilis in 204 patients (127 males and 77 females) who were treated for neurosyphilis between 1937 and 1952 at Rigshospitalet, Copenhagen. At the time of follow-up (1954-5), 155 patients were still alive, and on re-examination rather more than one half had signs of parenchymatous neurosyphilis, but only 24 showed evidence of syphilitic disease of the aorta, which was considered in eight of them to be "complicated"—having unmistakable signs of aneurysm or aortic insufficiency. At necropsy on the 49 patients who died, cardiovascular syphilis was found in seventeen (complicated in nine). The diagnosis of uncomplicated aortitis in living patients was based on the radiological finding of linear calcifications in the ascending part of the aorta. Thus in the series of 204 patients cardiovascular syphilis was demonstrated in 20 per cent. (complicated in 8.4 per cent. and uncomplicated in 11.7 per cent.). More males than females had syphilitic aortitis, especially the complicated

Comparison of the authors' figures with those of other workers from mixed groups of unselected patients with late syphilis indicated a similar incidence of cardio-vascular syphilis. The authors do not consider that the figures lend support to the view that syphilitic disease of the aorta runs a particularly mild course when it occurs in association with neurosyphilis. G. L. M. McElligott

Endemic Syphilis in Syria. (Endemische Syphilis in Syrien.) LUGER, A. (1958). *Derm. Wschr.*, 137, 25 and 57. 23 figs, bibl.

During the period 1954-6, the author took part in a campaign against endemic syphilis in Syria in which the local health authorities collaborated with the World Health Organization, and in this paper he describes the clinical and epidemiological findings. In all, 130,000 persons were examined, more than 49,000 of whom were suffering from endemic, non-venereal syphilis. Most of the patients lived in remote country districts, and one isolated area, in which 1,172 cases were observed, was selected for intensive study.

In over 90 per cent. of cases the disease had its onset before the age of 15 years. The infection is thought to spread through infected saliva, carried especially by the children's hands and fingers—the standard of hygiene is low and the chances of infection and superinfection accordingly very high. The earliest clinical manifestation was usually the appearance of multiple mucous patches in the mouth and generalized rashes on the body akin to those of secondary venereal syphilis. Only in five children did the author find single oral or laryngeal lesions, with regional adenopathy, which were probably primary sores. The incubation period from the time of infection to the onset of the secondary stage was observed in four cases and ranged from 2 to 6 months.

Leucoplakia with hyperpigmentation in the oral cavity was seen in about 20 per cent. of cases and is thought to represent a late manifestation of endemic syphilis, though no direct evidence of this could be obtained. Tabes and general paralysis were not seen, and the cerebrospinal fluid of 139 unselected patients was completely normal. No case of cardiovascular syphilis was found, nor was there any evidence of congenital syphilis. The most prominent late manifestations were bone lesions and gummata.

The author considers the absence of visceral involvement in endemic syphilis to be due to heightened immunity brought about by repeated subclinical superinfections, and the absence of congenital infection may possibly be due to protection of the placenta against infection in the same way. The difference between the two forms is thus largely determined by epidemiological factors. With improvement of hygiene, continuous exposure to infection will be curtailed and with it the transition of endemic syphilis into venereal syphilis becomes likely. [This hypothesis does not explain the occurrence, which the abstracter has observed, of typical syphilis with visceral manifestations in patients from endemic areas when they contract the infection venereally in the towns.]

Rheumatism and Tertiary Syphilis. Losada Losada, M. (1958). Rheumatism, 14, 49. 7 refs.

Complicated Syphilitic Aortic Aneurysms. Chand, D., Prashad, M., and Bharadwaj, B. M. (1957). *Indian Heart J.*, 9, 180. 14 figs, 14 refs.

Analysis of Fresh Cases of Syphilitic Infection. (Analiza przypadków świezych zakażeń kilowych W.R.) KOLANKOWSKI, J. (1957). Przegl. Derm. Wener., 253, No. 3.

General Paralysis in Africa. (Paralysie générale en milieu africain.) RAINAUT, J. (1958). Ann. méd.-psychol., 1, 209.

Asymptomatic Forms of Congenital Syphilis. (Formas asintomáticas de la neurosifilis congénita.) ORLANDO, J. C. (1957). Acta neuropsiquiat. argent., 3, 375. 10 refs.

General Practitioner and Syphilis. THOMAS, E. W. (1958). Illinois med. J., 113, 105.

Gumma of the Liver in Congenital Syphilis. WHITEHOUSE, D., and MACFARLANE, W. V. (1958). Arch. Dis. Childh., 33, 58. 2 figs, 12 refs.

SYPHILIS (Therapy)

Observations on Penicillin Therapy in Cardiovascular Syphilis. [In English.] KOULUMIES, R., and HEINIVAARA, O. (1957). *Acta med. scand.*, **159**, 453. 3 figs, 16 refs.

The decline in the incidence of early syphilis in Finland during the past 10 years is attributed to penicillin therapy, although preventive measures have also played their part. No such decline has been noted in the incidence of cardiovascular lesions, and this is attributed to the long latent stage preceding this phase of the disease.

In this paper from the University of Helsinki the authors describe the effects of penicillin treatment of 112 patients with cardiovascular syphilis (68 males, average age 50·3 years; 44 females, average age 54·3 years). The duration of infection in 31 cases ranged from 10 to 48 years (average 24). Most of the patients received 800,000 units procaine penicillin daily in one injection, but the total dosage varied greatly, from 3·2 million to 98 million units; no arsenic or heavy metal was given in the treatment of these patients. In a few cases there were mild Jarisch-Herxheimer reactions, and two patients with cardiac failure appeared to be made worse by treatment and died within 2 weeks.

At the start of treatment all the patients gave positive reactions to standard serological tests for syphilis. No change in these reactions was observed immediately after treatment, but of 29 cases in which serological tests were repeated a year or more later a significant decline in titre was noted in 21. A follow-up study of 54 patients 5 or more years after treatment revealed that only 23 survived. The most important factor influencing prognosis was the stage of the disease when treatment started. Of patients with uncompensated cardiac failure at the start, only 9 per cent. survived, compared with 60.6 per cent. of those who were fully compensated. There was no evidence that the prognosis was affected by the total dosage of penicillin given, nor that the results obtained with penicillin were, in general, definitely better than those achieved with older methods of treatment. Penicillin was considered to be the treatment of choice, however, because of ease of administration and lack of complications.

The authors emphasize [as many others have done] the importance of prevention of cardiovascular syphilis by the recognition and treatment of early syphilis. They also stress that adequate treatment of the heart condition is as important in cardiovascular syphilis as specific therapy.

A. J. King

Management of Syphilis. THOMAS, E. W. (1958). *Ohio St. med. J.*. **54.** 497.

SYPHILIS (Serology)

Treponemal Protein Antigens. Demonstration of an Antigen Common to Pathogenic and Reiter's Treponemes. (Sugli antigeni di natura proteica dei treponemi. Dimostrazione di un antigene comune al treponema patogeno ed al treponema coltivabile di Reiter.) DARDANONI, L., and CENSUALES, S. (1957). Riv. Ist. sieroter. ital., 32, 489. 21 refs.

Experiments were carried out at the Institute of Hygiene and Microbiology of the University of Palermo to elucidate the relationship between three types of protein antigen derived from treponemes:

- (1) The soluble protein antigen of Reiter's treponeme prepared by D'Alessandro's method [Riv. Ist. sieroter. ital., 1952, 28, 153];
- (2) A soluble protein antigen prepared from the Nichols strain of pathogenic *Treponema pallidum* by cryolysis and subsequent dialysis, first against ammonium sulphate solutions in increasing strength and then against buffered saline;
- (3) The complement-fixing antigen prepared by Portnoy and Magnuson [J. Immunol., 1955, 75, 348; Abstr. Wld Med., 1956, 19, 442] from Nichols strain by extraction with sodium deoxycholate, a specimen of which was supplied by one of the original authors.

In complement-fixation tests with human and rabbit syphilitic sera and antisera prepared in rabbits against the Reiter antigen the first two antigens reacted with all three sera, but the third only with the syphilitic sera and not with the anti-Reiter serum. Cross-absorption experiments were then carried out with the first two antigens on human syphilitic serum. Absorption with the Reiter antigen completely abolished the reactivity of the serum in subsequent tests with the same antigen, but had no effect on its reactivity with the pathogenic treponemal antigen. Absorption with the latter antigen, however, diminished the reactivity of the serum with both antigens. Reactivity with a cardiolipin antigen remained unaffected by these absorptions. Finally, cross-absorption experiments were carried out on human and rabbit syphilitic sera and immune anti-Reiter sera with suspensions of T. pallidum and of Reiter's treponeme. The results were not absolutely clear-cut, but it appeared that absorption with a suspension of Reiter's treponeme did not completely eliminate further reactivity in a complementfixation test with either the Reiter or the pathogenic treponemal antigen, whereas absorption of these sera with a suspension of T. pallidum completely removed the antibodies reacting with the pathogenic treponemal antigen, but did not completely eliminate those reacting with the Reiter antigen.

The authors conclude from these tests that T. pallidum and Reiter's treponeme share a common antigen. The failure of whole treponemal suspensions to remove this common antigen was probably due to the fact that the common (or group) antigen is situated more deeply in the bacterial cell and is thus "inaccessible". Evidence is quoted to show that such a "non-available" antigen may become accessible after prolonged storage of the treponemal suspension at $+4^{\circ}C$, suggesting the loss of some protective material.

Significance of the Disappearance of Treponemes in the Specific Diagnosis of Syphilis. (Die Bedeutung des Treponemenschwundes für die spezifische Luesdiagnostik.) Fegeler, F. (1957). Zbl. Bakt., I. Abt. Orig., 170, 66.

Nelson's treponemal immobilization (T.P.I.) test introduced a new era in serological testing for syphilis. It has been shown to be highly specific and reproducible in experienced hands, but the number of tests which can be carried out by one serologist is limited by the complicated technique and it is unlikely that the test will even become a routine one. Moreover, the present author believes that the test may give biological false results despite its admittedly high specificity.

The "immune adherence" phenomenon was originally described by Nelson himself during early observations on the T.P.I. test. In the present studies, carried out at the Wilhelm University, Münster, the author has compared the results of a "treponemal disappearance" test, based on the immune adherence phenomenon, with those of the T.P.I. test on 249 sera from untreated syphilitic patients, his criterion of positivity being the disappearance of 85 per cent. of the treponemes. The result of the T.P.I. test was negative in 119 cases and positive in 130. Of the 119 negative sera, the treponemal disappearance test gave a negative result in 118 and a doubtful result in one, while of the 130 T.P.I.-positive sera, the result was positive in 124, doubtful in three, and negative in three. The result of the T.P.I. test applied to the sera of 115 treated syphilitic patients was negative in 31 and positive in 84; of the former, the treponemal disappearance test result was negative in thirty and doubtful in one. while of the latter, it was positive in 74 and negative in ten. The author concludes that the treponemal disappearance test is useful in excluding syphilitic infection. but that in confirming such infection it is less specific than the T.P.I. test.

The test may also have a place in the clarification of socalled false T.P.I. test results. Thus in the examination of sera from 1,284 patients over a 2-year period the T.P.I. test gave a doubtful, false positive, or false negative result on 75 patients (5·8 per cent.), of whom 27 had been previously treated for syphilis and 48 had not. Of 39 of the 48 untreated cases in which a second T.P.I. test was performed, the result remained in doubt in eight, in all of which, however, the treponemal disappearance test gave a strongly positive result and the diagnosis of syphilis was confirmed clinically. In five cases giving a doubtful or negative T.P.I. reaction, a negative result by the treponemal disappearance test was considered to exclude the diagnosis of syphilis. The cause of false positive and false negative reactions is discussed and some technical details of the treponemal disappearance test are considered. The author concludes that the T.P.I. test remains the most specific and reliable aid to the diagnosis of syphilis in doubtful or difficult cases.

R. D. Catterall

Study of the Antigenic Structure of *Treponema pallidum* by Specific Agglutination. HARDY, P. H., and Nell, E. E. (1957). *Amer. J. Hyg.*, 66, 160. 2 figs, 16 refs.

Various tests have recently been introduced for the demonstration of specific antibodies to pathogenic treponemes in which whole treponemes are employed as the antigenic component. Discrepancies between the results of the several tests have suggested that different antigene-antibody reactions are involved in them, implying that *Treponema pallidum* has a complex antigenic structure.

The authors have therefore attempted to clarify this structure in experiments carried out at the Johns Hopkins University, Baltimore. Suspensions of killed treponemes from syphilomata of the testes of rabbits infected with the Nichols strain were used to obtain immune sera from adult animals. All Wassermann antibody was removed from these sera by absorption with beef heart preparations, ethylenediamine tetra-acetate (EDTA) was added to bind divalent cations, and agglutination tests were then performed with suspensions of *T. pallidum*.

Heating, reduction of pH, and the presence of divalent cations were found to affect the results. It was also found that freshly prepared treponeme suspensions were less readily agglutinated than suspensions which had been stored at 4°C. [This would suggest either the existence of a physical barrier (such as a capsule or slime layer) preventing the combination of antigen with antibody until it has been removed by enzyme or other action, or the presence of such a large quantity of surface antigen that all available antibody is absorbed by relatively few organisms.] Since a direct relation was demonstrated between agglutinability and antibody-combining capacity, however, the latter explanation can be excluded. The former explanation is supported by the finding of Turner and Hollander that the addition of hyaluronidase (or of factors hindering its inhibitors) increased the agglutinability of treponeme suspensions, indicating the existence of a mucopolysaccharide coat. Evidence is presented which suggests that syphilitic immune serum contains two specific antibodies, the antigenic component of the treponeme which reacts with one of these being inactivated by both heat and trypsin, whereas the other appears to be stable to these agents. The authors point out that while Portnoy's complement-fixation reaction, which is the only treponemal serological test that does not employ whole organisms, should for that reason approach most closely to a single antigen-antibody system, it is quite possible that, here too, multiple reactions are involved. Allene Scott

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Experience of the Nelson Test at the Skin Clinic of the Johannes Gutenberg University, Mainz. (Erfahrungen mit dem Nelson-Test an der Hautklinik der Johannes-Gutenberg-Universität, Mainz.) BARNISKE, R. (1957). Z. Haut- u. Geschl.-Kr., 23, 290. 2 figs, 21 refs.

The results obtained with the treponemal immobilization (T.P.I.) test of Nelson and Mayer, which has been in use for the last 3 years at the Johannes Gutenberg University Skin Clinic, Mainz, are reported. In untreated cases of early syphilis the result of the T.P.I. test becomes positive somewhat later than those of the standard tests for syphilis (S.T.S.). If the patient remains untreated the T.P.I. test result apparently continues to be positive throughout life, whereas the S.T.S. reactions may become negative. The S.T.S. gave non-specific positive reactions in about 45 per cent. of sera from a group of 220 patients suspected of having latent syphilis: on the other hand eight patients who gave a negative reaction to the S.T.S. gave a positive T.P.I. reaction and are described as suffering from "latent sero-negative syphilis". Several case histories are presented.

Reversal of the T.P.I. test result after treatment in cases of early syphilis occurred later than with the S.T.S. Such reversal is thus suggestive of cure, but the persistence of a positive T.P.I. test result after intensive treatment need not always necessitate further treatment. In the author's opinion the main use of the T.P.I. test is not to replace the standard reactions in routine clinical practice, but to detect non-specific positive and false negative results given by these tests.

[The diagnosis of asymptomatic syphilis depended in some of the author's cases solely on the presence of a positive T.P.I. test result and was incapable of further corroboration.]

G. W. Csonka

Specificity of the Skin Reaction and Its Prophylactic Significance in the Diagnosis of Syphilis. (Zur Spezifität der Kutanreaktion und ihre prophylaktische Bedeutung für die Luesdiagnose.) ROTTMANN, A. (1957). Int. J. proh. Med. (Stuttgart), 1, 56. 4 refs.

The author argues that the incidence of late manifestations of syphilis is increasing, but that in many cases these manifestations are masked and are difficult to diagnose. He restates his concept of "focal syphilis", in which the viscera, the nervous system, and the blood vessels are said to be principally attacked, and points out that the diagnosis is often missed in such cases. In his experience (in Vienna) skin tests with "luotest", an extract of syphilitic rabbit testes, are of great value in the diagnosis of such cases.

A mixed group of 45 patients was subjected to repeated cutaneous testing. In those with syphilis the cutaneous reaction often became positive within a few hours or days of the initial inoculation. In some cases in which serological reactions for syphilis were negative before testing there was a change to a positive reaction after the skin tests. In non-syphilitic patients repeated skin testing failed to produce positive reactions. In successfully treated cases which had become sero-negative, the cutaneous reaction was always negative. The author goes on to describe experiments which indicated that the active

component of the antigen used consists of an extract of the body of the spirochaete, together with a lipid. Positive reactions due to sensitization to rabbit testicular protein are considered to be unlikely. The author recommends this cutaneous test as a diagnostic method with wide application in clinical medicine.

[See comment on following Abstract] R. D. Catterall

Results of Investigations with Luotest in Asia. (Bericht über Untersuchungsergebnisse mit Luotest in Asien.) GRILLMAYR, W. (1957). Int. J. proph. Med. (Stuttgart), 1, 61. 2 figs.

At the General Hospital, Colombo, Ceylon, the author, greatly influenced by Rottmann's theories of "focal syphilis" and his use of intradermal tests as a means of diagnosing this rather obscure type of syphilis, has applied the skin test with "luotest" to a large number of patients. The results are presented in tabular form.

A special clinic called the "Island Clinic" has been set up and is attended by 150 to 200 patients a day. The author has coined the term "island disease" for the focal syphilis which he describes. He states that its clinical manifestations are often mistaken for hysteria and that mental symptoms resembling those of schizophrenia are frequent.

[Rottman's theories of "focal syphilis" (Herdlues) are not generally accepted in Great Britain or the U.S.A., where cutaneous tests alone are not considered to be reliable in the diagnosis of syphilis.] R. D. Catterall

"Autoimmune" Reaction against Human Tissue Antigens in Certain Acute and Chronic Diseases. I. Serological Investigations. Gajdusek, D. C. (1958). A.M.A. Arch. intern. Med., 101, 9. Bibl.

In this paper from the Walter and Eliza Hall Institute of Medical Research, Melbourne, the author reports the extension of investigations into auto-immune reactions in certain chronic diseases, of which a preliminary account has already been published [Nature (Lond.), 1957, 179, 666; Abstr. Wld Med., 1957, 22, 245]. In many cases of disseminated lupus erythematosus, chronic hepatitis, and certain other diseases, a reaction has been demonstrated between presumed auto-antibodies present in the blood and human organ antigens whereby complement fixation occurs. It is postulated either that components of human tissue might become antigenic because of some modification of their chemical pattern by viral, enzymatic, or toxic action, or that antigenic components normally inaccessible might conceivably be rendered accessible by such action to immunological processes.

Antigens were prepared by centrifugal clarification of saline suspensions of homogenates of many normal human tissues, though tests were carried out mainly with liver and kidney antigens. From the results obtained the sera tested fell into two groups. Of the first, consisting of 187 from healthy subjects and 152 from cases of various acute and chronic diseases, 3 per cent. gave positive complement-fixation reactions, in low titre, to liver antigens and 10 per cent. to kidney antigens. In the second, consisting of sera from 75 cases of hepatic disease (including

viral, postviral, lupoid and chronic nutritional hepatitis, and chronic biliary cirrhosis), 31 cases of collagen disease (including rheumatic fever, rheumatoid arthritis, acute glomerulonephritis, nephrotic nehpritis, and disseminated lupus erythematosus), and eight cases of multiple myeloma or macrog!obulinaemia, the proportions of sera which gave a positive complement-fixation reaction with one or other or both of these antigens were significantly higher, ranging from 27 to 100 per cent. Sera giving negative reactions with liver and kidney antigens generally also gave negative reactions with other tissue antigens, whereas those giving positive reactions with liver and kidney usually reacted also with all the other tissue antigens tested. High-titre reactions were found only in acute viral hepatitis, lupoid hepatitis, primary nonobstructive biliary cirrhosis, disseminated lupus erythematosis, and macroglobulinaemia.

Antigens prepared from liver, kidney, thyroid, and adrenal tissue were more stable on storage and more consistent in reaction, with higher titres, than those prepared from skeletal or cardiac muscle and spleen. Although all the muscle preparations tested were active antigenically, serum titres with different muscle antigens varied greatly, which was not the case with other antigens. No organ specificity was encountered, and sera which were highly reactive against human tissue antigens were equally so against tissue antigens from the rat. Both by precipitation and electrophoretic fractionation, the reactive substances were shown to be in the slow-moving γ -globulin fraction of the serum proteins. The antigenic components of kidney, liver, and muscle extracts were almost completely sedimented by centrifugation at 35,000g for 45 minutes, with the notable exception of one antigen in human liver extract. The macroglobulin separated from the serum of a macroglobulinaemic patient contained all the activity of that serum. No regular association could be established between the auto-immune complement-fixation reaction and a number of similar reactions such as the Wassermann, Kahn, and Weil-Felix; the heterophil antibody titres of all positively reacting sera were within the normal range.

The author's presentation of the results is followed by an extensive commentary and discussion [which is too condensed to be readily abstracted] and by a comprehensive bibliography. He concludes that "although it was not possible to prove that the auto-immune complement-fixation serum reagents are auto-antibodies evoked by an antigen stimulus rather than adventitiously reactive serum proteins, available evidence strongly suggests that they are classical antibodies."

Harry Coke
II. Clinical Correlations. Mackay, I. R., and Galdusek,

D. C. (1958). A.M.A. Arch. intern. Med., 101, 30. 2 figs, 29 refs.

The classic example of an auto-immune reaction is provided by syphilis, in which it is thought that lipids released from damaged cells become auto-antigens, evoking the anti-lipid antibodies which are detected by the

Wassermann and similar reactions. Since the possibility of such a mechanism has been recognized, many other disease conditions have been suspected of resulting from auto-aggressive immunological action, particularly those characterized by the production of abnormal antibodies or by changes in the reticulo-endothelial system. disseminated lupus erythematosus being outstanding among these. In the investigation reported here, the results of the auto-immune complement-fixation test [see previous Abstract] against human liver and kidney tissue antigens were studied in relation to those of numerous other laboratory tests and the clinical picture in a number of cases of hepatic disease, disseminated lupus erythematosus, and "paraproteinaemia" selected from among those used in the investigation reported in the previous paper.

The cases of disseminated lupus erythematosus were studied in the greatest detail, since it was in this disease that the complement-fixation titres were most consistently elevated. Of the twelve cases selected, in all of which the diagnosis was considered to be established, ten gave a positive complement-fixation reaction with both antigens. However, the titres were not correlated closely with the acuteness of the disease, its clinical course, or the distribution of the lesions, though serial observations suggested that suppression of the complement-fixation reaction occurred in parallel with symptomatic alleviation during cortisone therapy. No correlation was established with the results of other laboratory tests. Possible significance was attached to the frequent incidence of lymphoid collections in biopsy material in cases in which the complement-fixation titre was consistently high.

The cases of "paraproteinaemia" studied consisted of four cases of multiple myelomatosis and five of primary macroglobulinaemia. Three of the former and one of the latter gave negative complement-fixation reactions, while two of the latter gave very strongly positive reactions. The possibility is suggested that the positive reactions in this group were due to an abnormality in the essential processes of immune γ -globulin production. Serial estimations in the cases of viral hepatitis studied showed that in about 50 per cent. a positive complement-fixation reaction developed during the course of the disease, usually becoming negative on recovery. A high and persisting positive titre appears to be characteristic of both chronic postviral and lupoid hepatitis.

As the authors point out, "the results reported in this and the preceding paper are sufficient to raise an almost endless series of questions" requiring much further investigation.

Harry Coke

Treponema pallidum Agglutination Test for Syphilis: with Special Reference to Antigen Preparation. CAIN, R. M. (1957). Jap. J. exp. Med., 27, 289. 17 refs.

Congenital Biologic False-Positive Serologic Test for Syphilis. Cannon, J. F. (1958). A.M.A. Arch. intern. Med., 101, 620.